E11-02 Controversy in Small Cell Lung Cancer, Tue, Sept 4, 16:00 – 17:30

Controversies in the timing of chest radiotherapy

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Since the metaanalysis conducted by Pignon et al, chest radiotherapy is now a classical component in the treatment of limited small cell lung cancer. The next question is to define the optimal way of combining drugs and radiation including the drugs, the sequence and the characteristics of the radiation treatment (doses, volumes, fractionation and timing). So, the issue of timing is only one variable amongst different possibilities. This issue have been addressed by a series of randomised trials and metaanalysis.

Six randomised trials have addressed the question of the timing: 5 have used a concurrent chemo radiotherapy schedule while one used a sequential approach (Work). Trials are using a cisplatine based chemotherapy and a continuous irradiation (a split-course schedule was only used in the Work trial). The timing of chest RT varies from 42 to 169 days for the late group and during the first cycle of chemotherapy for the early group. Three trials are in favour of an early administration (Murray, Skarios, Jeremic) while 3 are in favour of a late chest RT (Spiro, Work, Perry). Except for Murray and Works trials, the late chest irradiation was delivered within 64 days and certainly not at the end of the chemotherapy programme. It is interesting to compare the results of Spiro and Murray trial with a very similar design but leading to different results: the Spiro trial favours the late chest RT while the Murray is in favour of an early administration. There are some differences in the treatment design: the timing of chest radiotherapy was respectively on day 22 and 105 for Murray trial and on day 1 and 64 for the Spiro trial The radiation schedule was also slightly different: 40 Gy in 15 fractions over 3 weeks for Murray and 50 Gy in 25 fractions over 5 weeks for Spiro. Nevertheless, chemotherapy compliance was certainly the main difference between the two trials: in Spiro trial, the six cycles of chemotherapy were given to 69% of the patients in the early RT vs. 80% for the late group while in the Murray trial there was no major difference between the two arms with a chemotherapy compliance over 80%. In general, the compliance to chemotherapy was reduced in most trials in case of the early chest RT (Skarios, Work, Perry).

Different metaanalysis have been conducted including some of those trials and other trials not especially design to study the timing but were a difference in timing was observed between the two arms (An alternating schedule vs. a sequential for the Gregor trial and an early concurrent approach vs. a sequential for the Japanese trial). The definition of early varies from one metaanalysis to another (from within one month or before the 3 cycles of chemotherapy).

In those metaanalysis, there was a trend in favor of an early radiotherapy when the non-platinum chemotherapy trials were excluded. In Fried metaanalysis including 7 trials, an early RT means an RT delivered within 9 weeks or before the 3 cycles of chemotherapy. A benefit in favor of an early chest RT was seen only for platinum based chemotherapy and for hyper fractionated radiation schedule. In the Cochrane analysis, only a trend was observed in favor of a chest RT delivered within 30 days after the start of chemotherapy after excluding the Perry trial. If 5-year data are taking into account, then thoracic radiation delivered within 30 days after the start of radiation increases the survival from 13.8 to 20.2% but at the expense of more acute toxicity, esophagitis and leucopenia.

Furthermore, reviewing the data available from randomized trial, De Ruysscher and Vansteenkiste introduced the SER concept: this is the time elapsed between the start of any therapy and the end of the radiation: in an analysis including 5 trials (Takada, Jeremic, Murray, Work and Turrisi), a short SER time let to a clear survival benefit This concept is based on the assumptions that the first cytotoxic insult may triggers an accelerated tumor repopulation and a more aggressive treatment is an important issue. It is interesting to notice that in Murray trial the radiation was an accelerated schedule 45 Gy in 3 weeks and in Turrisi trial the accelerated schedule (45 Gy in 3 weeks with 2 fractions a day) let to a clear survival advantage over the classical 45 Gy in 5 weeks.

In conclusion, there is certainly not a clear answer but the data may suggest a small advantage for a concurrent chemo radiotherapy approach and an early administration of chest radiotherapy. This implies to have an adequate patient selection including the extent of the tumor and the patient co morbidities, to avoid an excessive toxicity and to ensure a good compliance to the subsequent chemotherapy cycles. This raises another question: is the classical definition of limited disease the good one to help us to select the patient for an aggressive approach.

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E11-03 Controversy in Small Cell Lung Cancer, Tue, Sept 4, 16:00 – 17:30

Controversy in small cell lung cancer : targeted therapy

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For three decades, trials of new chemotherapy regimens for small cell lung cancer (SCLC) have failed to substantially improve clinical outcomes. The promise of targeted therapy has yet to be realised for SCLC but there is cautious optimism that there will soon be a breakthrough for this disease.

Angiogenesis Inhibitors : To date the majority of agents evaluated in SCLC have been inhibitors of angiogenesis. Trials of interferons conducted during the early 1990's were halted due to lack of significant benefit and toxicities that limited administration [1-4]. Trials of matrix metalloproteinase inhibitors also failed, and proved toxic due to musculoskeletal toxicity [5,6]. The first evidence that inhibition of angiogenesis may be a viable therapeutic strategy comes from the results of a randomised, phase III, placebo-controlled trial of maintenance thalidomide in patients with previously untreated extensive stage SCLC conducted by the French Intergroup [7]. The thalidomide treated group had a median survival of 11.7 months versus 8.7 months for the placebo group (HR: 0.48 [95% CI: 0.24-0.93]; p = 0.03). However toxic-

ity, principally neuropathy and constipation led to withdrawal from the study in just over half the patients who received thalidomide. In a phase III trial conducted by the London Lung Cancer Group a lower dose (100-200mg daily) of thalidomide has been evaluated in combination with etoposide and cisplatin but results are not yet available. Due to the toxicities observed with thalidomide and the success of bevacizumab (Avastin, Genentech, San Francisco, CA, USA), a humanized monoclonal antibody directed against the vascular endothelial cell growth factor (VEGF) in non-small cell lung and colorectal cancer, results from trials of this agent in SCLC are awaited with interest. Bevacizumab is generally well-tolerated although associated with increased risk of fatal haemorrhage, hypertension and thromboembolic events [8]. Vandetanib (Zactima, Astra-Zeneca, Macclesfield, UK), a small molecule oral inhibitor of VEGF receptor-2 tyrosine kinase, and to a lesser extent, epidermal growth factor receptor (EGFR) tyrosine kinase, is also well tolerated. The main side effects of vandetanib are thrombocytopenia, diarrhoea, rash and asymptomatic QTc prolongation [9]. A number of studies in SCLC are ongoing with these agents [10], some of which have completed recruitment. The National Cancer Institute of Canada - Clinical Trials Group have recently completed recruitment to a randomized phase II trial of vandetanib as maintenance chemotherapy in patients with SCLC with a response to first line treatment. A Cancer and Leukemia Group B (CALGB) study of cisplatin, irinotecan and bevacizumab in extensive stage SCLC, and a Sarah Cannon Research Institute trial evaluating carboplatin,irinotecan and concurrent radiotherapy followed by bevacizumab in limited stage SCLC have also completed recruitment. Other anti-angiogenic agents that are being evaluated include sorafenib (Nexafar, Bayer Pharmaceuticals, West Haven, CT, USA; Onyx Pharmaceuticals, Richmond, CA, USA), that is a multiple kinase inhibitor of Raf kinase, VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor beta and AZD2171 (AstraZeneca, Macclesfield, UK), an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, c-kit, platelet derived growth factor alpha and beta [10].

Growth and proliferation pathway inhibitors : Several studies identify c-kit tyrosine kinase signalling as a dominant pathway for growth that is upregulated in SCLC [11]. However, the clinical trials of imatinib (Gleevec, Glivec, Novartis, Basel, Switzerland; East Hanover, NJ, USA), a small molecule inhibitor of the c-kit tyrosine kinase, proved particularly disappointing. Negative results were first attributed to inclusion of patients with tumours that did not express the c-kit receptor [12], but imatinib subsequently failed in trials that selected for patients with c-kit positive tumours [13-15]. Also, a combination study of imatinib with irinotecan demonstrated higher than anticipated neutropenia, diarrhoea, and thrombosis likely due to decreased clearance of irinotecan in the presence of imatinib [16]. The potent efficacy of imatinib in patients with gastrointestinal stromal tumours is attributed to the presence of activating mutations in the c-kit tyrosine kinase domain. The rare occurrence of c-kit mutation in SCLC may account for the failure of imatinib in this disease. The EGFR inhibitor, gefitinib (Iressa, AstraZeneca, Macclesfield, UK), also failed in SCLC [17] but this is less surprising because over-expression of EGFR is infrequent in SCLC compared to non-small cell lung cancer. Temsirolimus (Wyeth Pharmaceuticals, Collegeville, PA, USA) inhibits the mammalian target of rapamycin (mTOR), a downstream mediator in the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway, leading to cell cycle arrest. A randomized phase II trial of temsirolimus maintenance conducted in patients with extensive stage SCLC was not conclusive for further evaluation [18]. Another strategy to inhibit growth signal transduction cascades in tumours is farnesyl transferase inhibition but this does not appear to be a feasible approach for SCLC [19].

Apoptosis promoters : Defective apoptosis underpins cancer cell survival and treatment resistance . The Bcl-2 family proteins are central regulators of apoptosis and Bcl-2 is overexpressed in 90% of SCLC [20]. Oblimersen (Genasense, Genta, Berkeley Heights, NJ, USA), an antisense oligonucleotide, is the first bcl-2 inhibitor to be tested in SCLC. In a phase I study, administration of oblimersen with carboplatin and etoposide was well tolerated with a response rate of 86% and time to disease progression of 5.9 months in patients with extensive stage disease [21]. Results from phase II evaluation are currently awaited. Several small molecule inhibitors of Bcl-2 family proteins are in preclinical development and will soon enter clinical trial. Notably, ABT-737 (Abbott Laboratories San Diego, California, USA) inhibits the anti-apoptotic proteins Bcl-2, Bcl-X(L) and Bcl-w, and has demonstrated unprecedented single agent activity in SCLC xenografts [22]. Other pro-apoptotic strategies include aplidine (Pharma Mar, Madrid Spain; Cambridge, USA), a novel marine cyclodepsipeptide that also has antiangiogenic properties. Aplidine is noted to cause muscle toxicity [23] and the results of phase II testing in SCLC are due to be reported soon. The 3-hydroxy-3methylglutaryl CoA reductase inhibitor simvastatin suppresses growth, induces apoptosis and enhances sensitivity to etoposide in preclinical studies of SCLC [24]. A phase III trial to evaluate the concept that statins combined with chemotherapy will improve on chemotherapy alone has recently opened in Great Britain and a phase II study is also open in South Korea [10]. Apoptosis has also been correlated with proteasome activity. Bortezomib is a proteasome inhibitor that has been approved for use in multiple myeloma. In SCLC cell lines bortezomib reduces Bcl-2 levels and induces apoptosis[25] but it is not active as a single agent in patients with extensive stage SCLC[26] and results from combination studies are awaited.

Perspectives and Future challenges : The development of targeted therapy for SCLC is proving frustrating. Although various targeted therapies have been evaluated, the majority of studies have been conducted in 'untargeted' populations[27]. Yet, strong preclinical data to pursue c-kit inhibition with imatinib did not translate to the clinic even when patients were selected for tumoural expression of c-kit. One caveat to using SCLC tumour for patient selection is the propensity for this disease to be exquisitively chemo / radiosensitive at presentation but substantially more resistant to treatment at relapse. Targets identified in chemonaive tumours may be irrelevant for previously treated tumours. Thus, greater understanding of mechanisms governing treatment resistance may be required to shape the future development of targeted therapy and aid in selection of the most appropriate agents to prioritise for trials in this disease.

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E11-04 Controversy in Small Cell Lung Cancer, Tue, Sept 4, 16:00 – 17:30

The role of irinotecan in the treatment of small cell lung cancer

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Since the 1960's, small cell lung cancer (SCLC) has been recognized as a distinct subtype of lung cancer with a unique sensitivity to chemotherapy (1). Multiple therapeutic agents and strategies tested over the last 3 decades result in a 1 year survival rate of 30-40% for patients with extensive stage disease (ED). Unfortunately, unlike other chemotherapy-sensitive cancers such as lymphoma and germ cell tumors, significant advances in the treatment of ED SCLC have stalled. Testing of "newer" chemotherapy agents such as epirubicin, ifosfamide, vinorelbine, the taxanes, and gemcitabine, have failed to improve survival compared with the older chemotherapy agents, cisplatin and etoposide (PE). In the U.S. PE for 4 cycles has been standard first line therapy based upon the results of randomized trials which indicated that other regimens were not superior, but rather resulted in more inconvenience and toxicity (2).

Camptothecin is a plant alkaloid present in the Asian tree Camptotheca acuminata. Camptothecin was recognized as a potential anti-cancer drug based upon a screening program conducted by the U.S. National Cancer Institute in the 1960's (3). During replication, DNA unwinds so that single strands serve as a template for synthesis of new DNA strands. Topoisomerase 1 plays a critical role in the cleavage of single DNA strands, necessary to allow the broken strand of DNA to rotate around the intact strand during DNA replication. Camptothecins target topoisomerase 1 by stabilizing the cleavable complex between topoisomerase 1 and DNA (4). Irinotecan, a water-soluble semi synthetic derivative of camptothecin, entered clinical trials in the 1980's. Irinotecan is a prodrug of the metabolite, SN38, which has 2-3 logs greater activity than irinotecan. Importantly, SN-38 is cleared by uridine diphosphate glycosyltransferase 1 family polypeptide A1 (UGT1A1), an enzyme important for biliary glucuronidation. Patients with certain polymorphisms in the promoter region of UGT1A1 are at higher risk for diarrhea and neutropenia (5).

In 2002, Noda et al reported the results of a phase III trial from the Japanese Cooperative Oncology Group (JCOG) that compared treatment with cisplatin plus either irinotecan or etoposide in 154 patients with ED SCLC (6). Median and 1 year survival was significant improved in the patients receiving the irinotecan-based regimen compared with PE (12.8 months vs. 9.4 months, 58.4% vs. 37.7%, respectively). Patients on the PE arm experienced more neutropenia and thrombocytopenia, while patients on the IP arm experienced more diarrhea. The study was discontinued early based upon the recommendation of a data monitoring committee. A phase III trial conducted in the U.S., Canada, and Australia, utilizing a different dose and schedule of irinotecan and cisplatin failed to confirm a survival advantage for the IP arm over the EP arm (7). Despite a change in the dose and schedule of IP, rates of gastrointestinal toxicity, namely vomiting and diarrhea were not substantially reduced, although dose intensity was improved compared with the IP regimen utilized in the JCOG trial. While there are several plausible reasons to explain the disparate results from the two trials, known pharmacogenomic differences between North American and Japanese populations likely played a role in determining both toxicity and efficacy profiles of IP. Specifically, polymorphisms in UGT1A1 are observed between patient populations. Low rates of Gilbert's syndrome (decreased level of gene transcription of UGT1A1) are recognized in Asian populations (8). In one study in non-small cell lung cancer, patients with Gilbert's syndrome experienced more toxicity and worse survival with IP (9). Differences in toxicity and efficacy profiles amongst North American and Japanese patients utilizing the same drugs have been reported (10). Similarly, UGT1A1*6 and UGT1A9*22 genotypes have recently been reported to be associated with irnotecan-related toxicity, response, and survival in Korean patients (11).

While PE remains standard in the U.S. for now, IP is an equally effective alternative regimen against ED SCLC. The substitution of carboplatin for cisplatin in the IP regimen has been explored in phase II and randomized phase II studies. Progression free survival favored

